


## The Pap Test

Potpourri Of Glandular & Miscellaneous Cells



George Papanicolaou

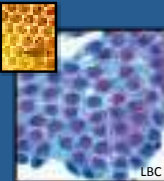

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 Director of Cytopathology  
 The University of Chicago

## The Pap Test

### Endocervical Cells in Health and Disease

### Classic Endocervical Cells




- Uniform, columnar cells
- Sheets, “honeycomb”
- Strips, “palisades”
- Single, N-C polarity
- Presence => TZ sampled

### Reactive Changes

Common in endocervical cells!

- Minimal crowding: cells “lay flat”
- Nuclear enlargement (up to 4-5x), hyperchromasia, multinucleation
- Round with smooth membranes
- Prominent nucleoli
- N/C ratios maintained
- Mitoses possible—but be careful!
- No apoptosis


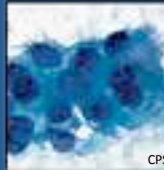
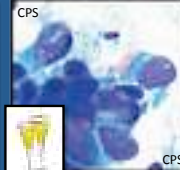




### Tubal Metaplasia

Common (normal)!  
Diagnosis usually easy:

- Ciliated cells!
- Champagne bubbles

But sometimes difficult...


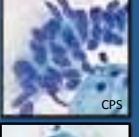





### Tubal Metaplasia

Can mimic AIS or CIS

- Hyperchromatic crowded groups
- Stratified, rosettes, feathering
- Enlarged, pleomorphic nuclei
- Dark, but fine even chromatin
- Mitosis, rare apoptosis

Pearls: Look for cilia, bubbles

### Atypical Glandular Cells

“Atypical cells, apparently glandular in origin, that are not readily classifiable as either reactive or neoplastic in nature”

Subcategories:

- Favor endocervical\*
- Favor endometrial\*
- Favor neoplastic
- Adenocarcinoma in situ
- Not otherwise specified

\*Specify cell of origin, if possible  
Follow-up: Colpo (+ EM Bx for AEMs)

AEMs: Atypical endometrial cells

### Atypical Glandular Cells ...causes are legion

High endocervical cells Reactive endocervical cells Endocervical brush artifact Endocervical repair Endocervical polyps Directly sampled EMs Lower uterine segment Cone biopsy artifact Endometriosis	Tubal metaplasia Microglandular hyperplasia IUD effect Postpartum atypia Arias-Stella reaction Squamous carcinoma: in situ, invasive Endocervical glandular neoplasia Metastatic adenocarcinoma
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### AGC: Worst of all worlds

Poor at identifying women with significant glandular abnormalities (low sensitivity)  
Includes *many* women without significant abnormalities (low specificity)  
Of lesions, many are squamous, not glandular  
Of cancers, most are endometrial, not cervical  
Some women have serious abnormalities!  
=> Requires careful clinical follow-up

AGC: Atypical Glandular Cells

### Atypical Endocervical Cells


Disorderly sheets, crowded 3D groups, microacini, ↑ N/C, nuclear enlargement, pleomorphism, irregular nuclei, granular chromatin, mitoses, apoptosis  
Not all need be present for diagnosis

Features favoring reactive changes:\*


- Distinct cell borders, nucleoli,
- no mitosis, no apoptosis

Features favoring neoplasia:

- More crowding, rosettes, feathering,
- coarse dark chromatin, high N/C,
- mitoses, apoptosis



AIS



CPS


\* "AGC, favor reactive" *not* used in actual diagnosis

### Atypical Endometrial Cells

Suggestive, not diagnostic, endometrial CA

2 key atypical features:


- Nuclear enlargement (> Intermediate nucleus)
- Prominent nucleoli



LBC

LBC: Chromatin, nucleoli more distinct  
No criteria: reactive vs neoplastic “atypia”  
Most do not have endometrial pathology, but risk increases with age

### Endocervical Adenocarcinoma



Abnormalities of:

- Architecture
- Nuclei

Cannot exclude invasion!

### Architectural Abnormalities

HCGs

Rosette

Crowding

Strip

### Nuclear Abnormalities

Enlarged, elongated  
Coarse dark chromatin

High N/C, irregularities

Mitosis

Apoptosis

CPS

LBC

CPS

LBC

Crowding  
Enlargement  
Elongated or irregular  
High N/C ratio  
Coarse, dark chromatin\*  
Inconspicuous nucleoli\*  
Mitosis  
Apoptosis

\*in conventional Pap smears

### 4 Features Suggest Invasion

Increased single cells

Irregular chromatin

Prominent nucleoli

Tumor diathesis

*Pap test cannot exclude invasion!*

### Variants of EC Adenocarcinoma

Villoglandular

Adenoma malignum

Signet ring

Clear cell

Adenosquamous

Glassy cell

CPS

CPS

CPS

CPS

CPS

CPS

### Endocervical "No No's"

**NO** crowding, piling up  
Should "lie flat"

**NO** microacinar formations  
No true glands!

**NO** elongated or irregular nuclei  
Can be big, but should be round

**NO** mitotic figures  
Except repair, tubal metaplasia

**NO** apoptosis  
OK in endometrial cells

### The Pap Test

## Endometrial Cells in Health and Disease

### Endometrial Glandular Cells

Small clusters (HCGs)  
Degenerated small cells

**Nucleus:**  
~ Intermediate nucleus  
Round to irregular, single  
Small nucleoli (LBC)

**Cytoplasm:** Scant, basophilic,  
± vacuoles, neutrophils

Cilia => tubal metaplasia

**Wreaths:** Exodus (days 6-10)

Normal finding 1<sup>st</sup> half of menstrual cycle

### Endometrial Stromal Cells

**Superficial stromal cells**  
"Sticky histiocytes"  
Express CD68

**Deep stromal cells**  
Round to spindle  
Small oval nuclei  
Scant cytoplasm  
Express CD10

### Directly Sampled Endometrium

**EMs at any time of cycle**  
-Endocervical brush  
-Cervical endometriosis  
-Cone biopsy artifact  
Not reported as "Other"

**Hormonally responsive:**  
Mitosis, apoptosis, atypia, HCGs  
DDx: Epithelial abnormality

**Diagnostic Clues:**  
Orderly, uniform cells  
Biphasic (glandular-stromal)  
Capillaries in stroma  
Cilia if present

**No:** Frankly malignant cells,  
feathering, rosettes, diathesis

### Endometrial Cells in Women ≥40 Years

Spontaneously shed, *not directly sampled*, endometrial cells  
Usually benign finding, but risk of EM pathology increases with age  
Age selected as criterion, other data, eg, LMP, unreliable  
General category: Other  
Should specify if NILM  
*Atypical EMs are always abnormal!*

### Some Causes of Abnormal Shedding

Postpartum, abortion, IUD  
Instrumentation  
Hormonal therapy: OCPs, HRT  
Dysfunctional uterine bleeding  
Submucosal myoma  
Endometrial polyp  
Tuboendometrial metaplasia  
Endometrial hyperplasia  
*Endometrial carcinoma\**  
\*Risk increases after age 40

### IUD Effect

Endometrial cells any time of cycle

- Clusters of epithelial cells  
"Atypical" glandular cells in clean background  
-mimics metastatic AdCA  
Dx AdCA cautiously with IUD
- Single endometrial cells  
-mimic CIN 3  
Dx ASC-H may be safer  
Clues: Actinomyces, ameba, Hx!

### “Atypical Endometrial Cells”

Suggestive, not diagnostic,  
of endometrial carcinoma

No criteria to distinguish  
reactive from neoplastic  
endometrial cell atypia

### Atypical Endometrial Cells

Shedding AEMs is always abnormal\*

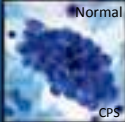
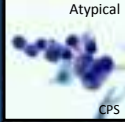
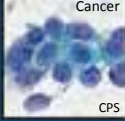
Two key atypical features

- Nuclear enlargement (> Intermediate nucleus)
- Prominent nucleoli

LBC: Chromatin, nucleoli more distinct  
→ unnecessary atypical interpretations

No criteria: reactive vs neoplastic “atypia”

\*Significant risk factor postmenopause

### Endometrial Carcinoma

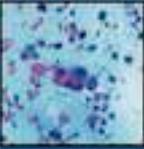
Cells: Uniform, round-oval, 10-15µm  
Nuclei: Round-irregular

Increase with grade:

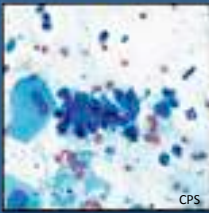

- Nuclear size
- Hyperchromasia
- Chromatin granularity
- Nucleolar size

Cytoplasm: Scant or vacuolated  
Leukophagocytosis typical (not diagnostic)

Background: Numerous histiocytes  
Low grade: Water diathesis, high maturation  
High grade: Tumor diathesis, atrophy

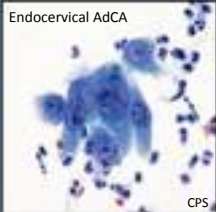
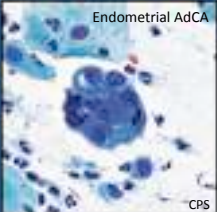


### Endometrial AdCA

Low Grade
High Grade

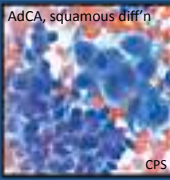
### Endocervical vs Endometrial CA


Favors endometrial origin:

- Fewer, smaller, rounder cells
- Smaller nuclei
- Less cytoplasm + PMNs


### Some Variants of EM CA




AdCA, squamous diff'n



Serous AdCA



Clear Cell AdCA



Secretory AdCA



### DDx: Arias-Stella Reaction

 Arias-Stella CPS	 Radiation CPS
 Chemotherapy CPS	 Clear Cell CA CPS

### Decidual Cells

Cervical stroma decidualizes early in pregnancy  
 Decidual cells:  
 Parabasal sized  
 Large nuclei  
 DDx: Dysplasia  
 Chromatin bland, + nucleoli

LBC

CPS

LBC

### Trophoblasts

CPS

CPS

Pomegranate

Cytotrophoblasts      Syncytiotrophoblast

From placenta: occur rarely in late pregnancy/postdelivery  
 Not reliable indicators of adverse pregnancy outcome  
 If numerous or atypical, suspect trophoblastic disease

### Cocklebur (in a Pap Test?!)

Pregnancy associated, not specific  
 Radiate crystals, histiocytes  
 Nonimmune glycoprotein, lipid, + calcium deposited on biologically inert substances  
 Not hematoidin or Actinomyces  
 No effect maternal/fetal prognosis

CPS

### Small Cell Neuroendocrine Carcinoma

CPS

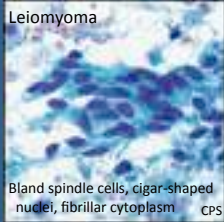
CPS

Aggressive, no precursor, HPV+ (most = 18)  
 Cyto: Like pulmonary counterpart  
 Immuno: Epithelial/neural mrks; 33% TTF-1 +  
 DDx: Met lung CA; other small celled entities  
 Pts often have squamous or glandular lesions

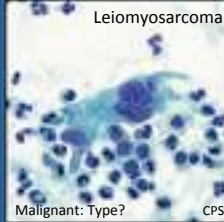
### Mesenchymal Tumors

Most are spindle cell neoplasms  
 Cells: Predominantly single, "ugly"  
 Nuclei: Can be very abnormal  
 Cytoplasm: Glassy or fibrillar  
 DDx: Benign mesenchymal tumor  
 Degeneration → abnormal chromatin (smudgy)  
 Ulceration (to shed) → Necrosis/inflam'n ~ tumor diathesis  
 Leiomyosarc + Stromal Sarc = 90% cases  
 Botryoid rhabdomyosarcoma in girls

### Smooth Muscle Tumors




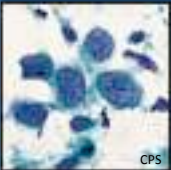

Leiomyoma  
Bland spindle cells, cigar-shaped nuclei, fibrillar cytoplasm CPS




Leiomyosarcoma  
Malignant: Type? CPS

Caveats: Leiomyoma can be atypical  
 Leiomyosarcoma can be bland  
 Final diagnosis based on *histologic* analysis:  
 Cellularity, nuclear atypia, mitotic count  
 DDx: Uterine trauma, eg, child birth

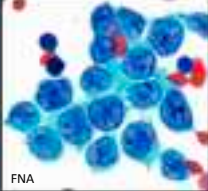

### Endometrial Stroma Sarcoma



Cyto: ~ Benign stromal cells  
 Clue: "Too many (stromal) cells" with mild cytologic atypia

### Rhabdomyosarcoma (Botryoid Sarcoma)


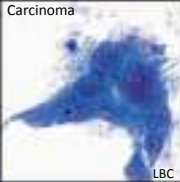



Classic "small blue cell tumor" of childhood  
 In FGT, spindle + strap cells (rhabdomyoblasts)  
 Myxoid background ± bizarre cells  
 Immuno: Desmin, MSA, myoD1, myogenin



FGT: Female genital tract

### MMMT

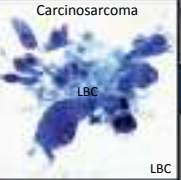
**Carcinomatous elements**  
Often serous carcinoma

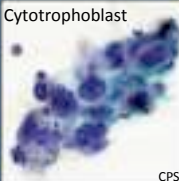
**Sarcomatous elements**  
 -Homologous: eg, Stromal, leiomyo-sarc  
 -Heterologous: eg, Rhabdomyo-, chondro-Sarcoma derived from epithelium by metaplasia


**Carcinosarcoma**



### Choriocarcinoma



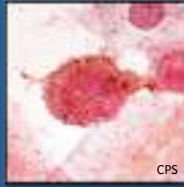
Cytotrophoblast  
CPS



Syncytiotrophoblast  
CPS

Trophoblastic, Germ Cell, Dedifferentiation  
 Biphasic proliferation:  
 ■Cytotrophoblast: Malignant component  
 ■Syncytiotrophoblast: Differentiated cytotrophoblast

### Melanoma



5-10% of melanomas arise in FGT (cervix rare)  
 -Metastatic melanoma more common  
 Few detected by cytology; misdiagnosis common  
 Helps if clinician mentions the funny, pigmented lesion seen on pelvic exam!  
 DDX: Many tumors, also benign nevi

### Lymphoma



Pap test: Often false (-) or wrong  
 Endometrial CA, H SIL/SCC  
 Sometimes suggests lymphoma  
 Single cells, morphology, LGBs  
 Large B cell most common  
 DDX: Follicular cervicitis, other small cell tumors  
 Be cautious in diagnosis without a mass lesion!

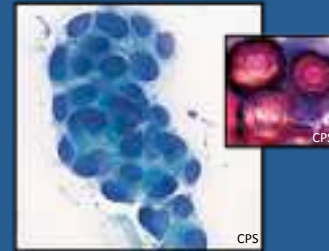
LGBs: Lymphoglandular bodies

### Metastases



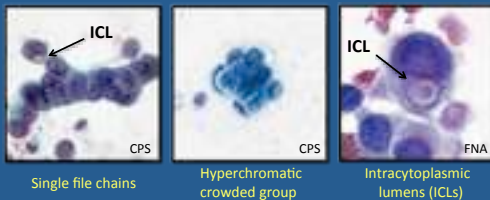
Cells often clearly malignant looking  
 Background: Clean (no diathesis), like "floater"  
 Consider metastasis if unusual morphology  
 Ovary most common source

### Ovary



Papillae or psammomas suggest ovarian origin  
 = most common tumor to metastasize to cervix

### Breast



Single file chains

Hyperchromatic crowded group

Intracytoplasmic lumens (ICLs)

### Signet Ring Cell Carcinoma



Usually Gastric CA  
 also breast, other GI



### Colorectal Carcinoma

1. Columnar cells
2. Cigar shaped nuclei
3. "Terminal bars"  
(Striated border, arrows)
4. Dirty necrosis

### Fallopian Tube Carcinoma

J. Ernest Ayre, 1947  
1<sup>st</sup> Reported in Pap Test

### Male Cells

Sperm

Seminal Vesicle

Generally not reported  
Note biphasic staining of head  
DDx: *Candida* spores  
Neutrophil lobes

"Ugly cells" with big, dark nuclei  
DDx: Malignancy  
Clues: Lipochrome pigment, smudgy chromatin, sperm

### Ferning of Cervical Mucus

Occurs near ovulation

### Curschmann Spiral

Intrinsic property of mucus

### Fistulae

Melamed-Wolinska Bodies

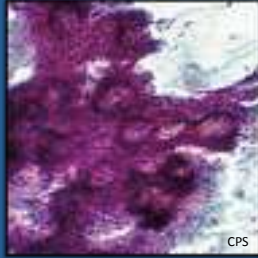
Rectal cells

Urothelial cells  
Watery discharge (p)

Fecal matter (caca)

Vesicovaginal fistulae      Rectovaginal fistula

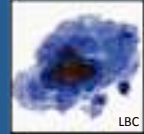
### Neovagina



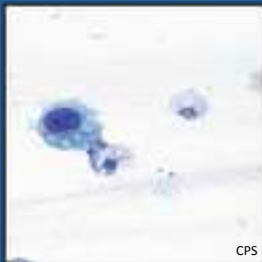
Skin or intestine can be used (colonic epithelium illustrated)  
Surveillance to detect inflammatory and neoplastic lesions

### Psammoma Bodies

Rare findings in Pap tests  
Benign associations ( $\geq 50\%$  cases)  
eg, IUD, OCPs, infection  
 $\pm$  Atypical cells  
Malignant associations  
eg, Papillary serous CA  
Cause not found in many cases



### Ciliocytophthoria Detached ciliary tufts



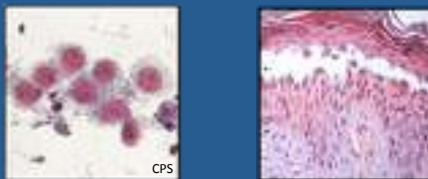
Nonspecific degenerative change  
...not ciliated parasites!

### Collagen Ball



In Pap test: From peritoneal cavity  
transit Fallopian tube  
(Common in peritoneal washings)

### Pemphigus Vulgaris



Autoimmune destruction of desmosomes  
→ suprabasilar blister with Tzanck cells  
Pitfall: Atypia + single cells mimics carcinoma  
Pearl: Repair-like (fine chromatin, smooth nuclei),  
perinuclear acidophilia, and clinical history!

Thank you!